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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/696,464	10/29/2003	Mathai Mammen	P-142-US1	5983

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EXAMINER	
PERLINGER, SARAH E	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 05/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/696,464	MAMMEN ET AL.	
	Examiner	Art Unit	
	Sarah E. Perlinger	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/14/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-46 are pending.

2. ***Election/Restrictions***

Applicant's election with partial traverse of Group I in the reply filed on March 28, 2006 is acknowledged. The traversal (of Groups I-IV) is on the grounds that it is improper to require restriction of the members of a Markush group unless the subject matter in the claim lacks unity of invention. This is not found persuasive with regard to groups III and IV because in the instant case, the compounds of groups I and III-IV are classified separately as illustrated in the restriction requirement sent March 20, 2006 and it would be extremely burdensome to search such diverse core structures. Each independent core structure is classified separately and requires a separate search in the electronic databases. Furthermore, compounds having the biphenyl piperidine carbamoyl core structure of the instant claimed compound can be utilized to treat conditions other than those delineated in the instant application and therefore, a reference anticipating or rendering obvious, one of the inventions of groups I and III-IV would not necessarily anticipate and/or render obvious, any of the other inventions of groups I-IV. Markush practice clearly delineates that for proper Markush grouping compounds of the group must (1) share a common utility, and (2) share a substantial structural feature essential to that utility (see MPEP 803.02, *In re Weber*, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and *In re Haas,* 580 F.2d 461, 198 USPQ 334 (CCPA 1978). In the instant case, the biphenyl piperidine carbamoyl core has been disclosed to have utility for treating allergic disorders while the biphenyl pyrrolidine carbamoyl core is recognized in the art to have muscarinic antagonistic activity, thus, a different utility (see Walsh et al., J. Med. Chem., 1989, 32, pages 105-118, especially page 109 compound 102 and page 108, compound 72). The lack of common core is proper for restriction and separate examination.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn

process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

In the instant case, in the event that the product claims are found allowable, process claims directed to a method of treating disease (i.e. claims 40-41, 43) will be considered for rejoinder. Claim 42, drawn to a biological assay, classified in class 435, will not be considered for rejoinder.

The restriction requirement with regard to groups I and III-IV is still deemed proper and is therefore made FINAL. However, groups I and II (Claims 1-33, 39, 44-46 as they are drawn to a compound of formula I wherein p=1) will be examined on the merits.

3. ***Claim Objections***

Claim 39 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claim has not been further treated on the merits.

4. ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 34-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is indefinite where it recites a protected "derivative" thereof. The word "derivative" is

improper because there are no boundaries for what a derivative would encompass and therefore the scope of claims 34-38 cannot be ascertained.

5. Claim 40 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is indefinite where a method for treating a mammal having a "medical condition alleviated by treatment with a muscarinic receptor antagonist" is claimed. It is unclear what a "medical condition alleviated by treatment with a muscarinic receptor antagonist" may include or exclude. The scope of claim 40 cannot be ascertained because of the vague terminology used.

6. Claim 40 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01(a) "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." The factors to be considered herein are those set forth as the In re Wands, 8 USPQ 2nd 1400 (1988) decision.

Nature of Invention

Claim 40 is drawn to a method for treating such a diversity of disorders for example as overactive bladder, Parkinson's disease, Alzheimer's disease, etc. in a mammal comprising administering a therapeutically effective amount of a compound of claim 1. No nexus exists among the diversity of such disorders which have multiple and unrelated etiology.

The State of the art and Predictability

Treating a neurological disorder such as neurodegenerative disease, including those such as Alzheimer's disease, Parkinson's disease, etc. has been well recognized in the art to be literally

untreatable (see CA 126:324757). In addition, in so far as neuropathies are concerned, it is well recognized that many neuropathies have different etiology and treatment of such conditions is highly specific. In absence of specific description of enablement, one skilled in the art is unable to operate such process (see CA 127:174580).

Furthermore, for the CNS related neurological disorders, it is a well-known fact that any compound having CNS efficacy must cross the blood brain barrier. No description for the instant claimed compounds having the ability to cross the blood-brain barrier has been provided.

The amount of guidance and working examples

No data or examples were provided for the compound as claimed in claim 1 illustrating which compound was effective with respect to specific neurological disorders in order to guide one having ordinary skill in the art to pick and choose for the individual method of treatment. In view of the absolute requirement for a compound to cross the blood-brain barrier in order for it to have efficacy in the CNS, no description or enablement can be found that the claimed compound would have any practical CNS method of use.

The specification provides none of the composition or dosage preparation or guidelines for a CNS route of administration, i.e. no guidance was provided in the specification for intracranial administration (see Specification, pages 46-51).

There isn't any one etiological mechanism that can treat such a diversity of diseases as those encompassed in the scope of the instant claim 40. Also, there is no nexus between antagonizing the muscarinic receptor to the treatment of such a diversity of disorders for example as overactive bladder, Parkinson's disease, or Alzheimer's disease in a mammal. No support was found that any of the compounds are able treat any pathology or symptom, nor was any pathology or symptom inexorably linked to antagonism of muscarinic receptors at any specific IC_{50}.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-41, 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01(a) "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". The factors to be considered herein are those set forth as the In re Wands, 8 USPQ 2nd 1400 (1988) decision.

Nature of Invention

The claims are drawn to a method for treating a mammal or patient having overactive bladder.

The state of the art and predictability

The state of the art in the pathophysiology of bladder dysfunctions is not well understood. "Neither of the mechanisms underlying the physiological functions of the bladder, to store urine at low pressure and to empty its contents at regular intervals, are still fully understood" (Boselli et al., J. of Autonomic Pharmacology, 2001, 21, page 219, Introduction). Furthermore, the role of acetylcholine, of which muscarine is a subtype, in bladder dysfunctions is not well understood in the art. "Thus it is likely that alteration of the neural acetylcholine control can play a critical role in pathological states. Such an exciting suggestion, however, remains to be validated also because the experimental approaches are often limited by the low availability of human urinary bladder specimen" (Boselli et al., J. of Autonomic Pharmacology, 2001, 21, pages 220, second column). Also, animal model testing has not been sufficiently established in the art to allow extrapolation of data from animal testing to humans. "There is no certainty whether or not urodynamic recordings from experimental animals resemble urodynamic

findings in humans with unstable bladders or are likely to be sufficiently close to justify the assumption that instability has been induced" (see Boselli et al., J. of Autonomic Pharmacology, 2001, 21, page 223, second column). Finally, it has been established in the art that muscarinic subtype selective antagonists have not been successful in the pharmacological treatment of bladder disorders (see Boselli et al., page 226, column 1).

The amount of guidance and working examples

The specification is limited to *in vivo* testing of compounds in a rat bladder and an *in vivo* rat salivation assay (see Specification, pages 104-106). ID50 values for test compounds' ability to inhibit rhythmic volume-induced bladder contractions were taken. No support was found in the specification for the treatment of overactive bladder being inexorably linked to any ID50 value.

In view of the high degree of unpredictability with regard to the pathophysiology of bladder dysfunction and the exclusive data of only one compounds' *in vivo* activity in rats, the specification has not offered guidance to support such diversified core compounds as claimed in the instant application, especially because the different cores have been shown to have different utilities, in the methods that are claims 40-41, 43. Furthermore, the specification fails to delineate the site of administration for treatment and the particular dosage of any compound, which is an effective amount for a particular disease state. One with ordinary skill in the art at the time of invention has not been offered guidance in how to make and/or use the methods of claims 40-41, 43.

8. ***Double Patenting***

Claims 44-46 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 33-35 of copending Application No. 10/888855. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to the copending claims when a process of preparing a compound of formula I is claimed.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The instant claims 44-46 are commensurate in scope with copending claims 33-35 of Application No. 10/888855. The only difference between the instant claims and the copending claims is that instead of W,X,Y and Z of formula I and V being only CH or CR4, W,X,Y and Z of formula I and VIII of the instant claims can be CH, CR4, N, or N-O provided that at least one of W,X,Y or Z is N or N-O. The aromatic/heteroaromatic ring containing W,X,Y and Z, however is a non-participating group at a non-participating site of the reactant. Therefore, slightly altering the aromatic/heteroaromatic group would not have a significant effect on the reaction overall. One having ordinary skill in the art in possession of Application No. 10/888855 would be in possession of the instant claimed process **because** the starting material of the reaction has been disclosed and therefore, it would be expected that the disclosed process would yield the product of formula I.

9. Claims 1-6, 13-33, 39-41, 43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8-9, 12-15, 20 of copending Application No. 10/975657 in view of claims 1-6, 13-22, 28-32 of copending Application No. 10/888855. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to the copending claims when q=m=n=0, Re is hydrogen and the claimed compound is in the form of a pharmaceutically acceptable salt.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The instant claims 1-6, 13-33, 39-41, 43 are broader than the claims 8-9, 12-15, 20 of copending Application No. 10/975657. The difference between the instant claims and the copending claims is that instead of p being only 1, p of the instant claimed compound can be 1 or 2 and instead of b being only 0, b of the instant claimed salt can be 0 or 1. Claims 1-6, 13-22, 28-32 of copending Application No. 10/888855 however teach a structurally similar compound wherein p is 1 or 2 and b is 0 or 1 (see for Example, page 111, claim 1). One having ordinary skill in the art in possession of claims 8-9, 12-15, 20 of copending Application No. 10/975657 and Claims 1-6, 13-22, 28-32 of copending Application No. 10/888855 would be in possession of such modifications as p being 1 or 2 and b being 0 or 1 **because** such modifications have been clearly guided to one skilled in the art in these references by exemplification of other analogous compounds. Both references teach structurally similar pharmaceutical compounds having utility as muscarinic receptor antagonists (see 10/975657, claim 14 and 10/888855, claim 30). Furthermore, success in using the structurally similar compounds as muscarinic receptor antagonist was demonstrated in Application No. 10/888855 (see Specification, pages 104-107). One having ordinary skill in the art would be motivated to make such modifications knowing that reasonable success has been demonstrated in analogous compounds. It is prima facie obvious to modify one known compound with attributes proven in analogous compounds.

10. Claims 7-12, 30, 39-41, 43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8-9, 12-15, 20 of copending Application No. 10/975657 in view of claims 7-13, 28, 29-32 of copending Application No. 10/888855. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to the copending claims when q=m=n=0, Re is hydrogen and the claimed compound is in the form of a pharmaceutically acceptable salt.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The instant claims 7-12, 30, 39-41, 43 are broader than claims 8-9, 12-15, 20 of copending Application No. 10/975657. The difference between the instant claimed compound and the copending compound is that instead of R2 being only a C1-C4 alkyl group, R2 of the instant claimed compound is a C1-C4 alkyl group or a CH2-cyclic group. Claims 7-13, 28-32 of copending Application No. 10/888855 however, teach a structurally similar compound wherein R2 is a C1-C4 alkyl group or a CH2-cyclic group (see for example, page 111, claim 7 and page 108, claim 1). One having ordinary skill in the art in possession of claims 8-9, 12-15, 20 of copending Application No. 10/975657 and Claims 7-13, 28-32 of copending Application No. 10/888855 would be in possession of such modification as R2 being a CH2-cyclic group **because** such modification has been clearly guided to one skilled in the art in these references by exemplification of other analogous compounds. Both references teach structurally similar

pharmaceutical compounds having utility as muscarinic receptor antagonists (see 10/975657, claim 14 and 10/888855, claim 30). Furthermore, success in using the structurally similar compounds as muscarinic receptor antagonist was demonstrated in Application No. 10/888855 (see Specification, pages 104-107). One having ordinary skill in the art would be motivated to make such modifications knowing that reasonable success has been demonstrated in analogous compounds. It is prima facie obvious to modify one known compound with attributes proven in analogous compounds.

11. ***Conclusion***

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Sarah E. Perlinger, whose telephone number is (571) 272-5574. The examiner can normally be reached on Monday through Friday, 8:30 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Thomas McKenzie, can be reached at (571) 272-0670. The fax number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

05/18/2006

Celia Chang
Primary Examiner
Art Unit 1625